REMARKS

Applicant has amended claims 14-18, 20-31, 33 and 34 in order to address the examiner's comments at the beginning of page 2 of the office action and the indefiniteness rejections. Applicant also adds claims 35-37. Upon entry of this amendment, claims 14-18, 20-31 and 33-37 will be pending. The office action is discussed below.

The claims are readily understood by the person skilled in the art

For definiteness, a claim need only reasonably apprise those skilled in the art of the utilization and scope of the invention. *Hybritech, Inc. v. Monoclonal Antibodies,* 231 USPQ 81, 94-95 (1986). Words are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Claims are to be given their broadest reasonable interpretation consistent with applicants' specification. *See* MPEP § 2111 (August 2001). In sum, in order to reject the claims on definiteness grounds, it is incumbent on the examiner to show how and why the skilled person having applicants' specification would not be apprised of the invention by the language-at-issue. The phrases rejected by the examiner are discussed below.

Citrated plasma and citrate-containing plasma fraction:

The examiner asserts that the claims are confusing due to the recitation of a "citrated plasma and citrate-containing plasma fraction." Applicant traverses this rejection.

A citrated plasma and citrate-containing plasma fraction are not products of the recited methods, but rather are starting materials. Thus, a practitioner starts with a citrated plasma and/or a citrate-containing plasma fraction, conducts the recited exchange, recovers at least one plasma protein and then finishes it to form a medicament. Thus, the resulting medicament will be substantially free of citrate ions or citrate-bound metals in order to satisfy the objectives of the invention, namely to provide a pharmaceutical that will contain less contaminating metal than others in the art. See pages 1-4 of applicant's specification. Preferred maximum levels of metals are set forth at page 12 of applicant's specification. Applicant submits that the skilled person would immediately comprehend these concepts, and therefore the claims are definite. Applicant therefore requests withdrawal of the rejection.

Optionally:

The examiner considers the term "optionally" to be indefinite. However, the term "optionally" is considered definite where the alternatives are clearly set forth in the claim. See MPEP § 2173.05(h)(III) (August 2001). In the instant situation, citrate is exchanged and if citrate-bound metals are present, those are exchanged

too. If citrate-bound metals are not present, then such metals are not exchanged. Applicant submits that this is clear to the skilled person, and therefore the rejection should be withdrawn.

Does not take up any undesired metals:

Applicant has clarified the metals to be the "undesired metals" previously defined in the claim. The reduction or absence of such metals can be determined by known methods, such as atomic absorption spectroscopy. See page 12, lines 5-6. Applicant therefore requests withdrawal of the rejection.

Non-precipitating:

The use of non-precipitating conditions allows for a more thorough exchange of citrate. See page 6, second full paragraph of applicant's specification. The determination of such conditions is readily ascertained by the skilled person. Exemplary concentrations and conditions are set forth at page 9 of the specification. Applicant submits that the skilled person can readily ascertain what is meant by this phrase and has the skill to achieve it. Accordingly, this phrase is not indefinite and the rejection should be withdrawn.

The claimed invention is not taught by the prior art

On pages 3-4 of the office action, the examiner repeats the rejection of claims 14-17, 20-23, 26, 28, 31, 33 and 34 as anticipated by U.S. Patent No.

5,561,115. On pages 4-5, the examiner repeats the rejection of claims 14-16, 18, 20-23, 28, 29, 31, 33 and 34 as anticipated by U.S. Patent No. 5,372,997. Applicant respectfully traverses these rejections.

Applicant notes that in order to reject a claim under 35 USC § 102, the examiner must demonstrate that each and every claim term is contained in a single prior art reference. *See Scripps Clinic & Research Foundation v. Genentech, Inc.*, 18 USPQ2d 1001, 1010 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 90 (Fed. Cir. 1986); *see also* MPEP § 2131 (August 2001). Claim terms are to be given their plain meaning as understood by the person of ordinary skill in the art, particularly given the limitations of the English language. *See* MPEP §§ 707.07(g); 2111.01 (August 2001). Claims are to be given their broadest reasonable interpretation consistent with applicant's specification. *See In re Zletz*, 13 USPQ2d 1320, 1322 (Fed Cir. 1989) (holding that claims must be interpreted as broadly as their terms reasonably allow); MPEP § 2111 (August 2001).

Not only must the claim terms, as reasonably interpreted, be present, an allegedly anticipatory reference must enable the person of ordinary skill to practice the invention as claimed. Otherwise, the invention cannot be said to have been already within the public's possession, which is required for anticipation. *See Akzo, N.V. v. U.S.I.T.C.*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986); *In re Brown*, 141 USPQ 245, 249 (CCPA 1964). Applicant discusses the references with these concepts in mind.

With regard to the '115 patent, the examiner states that the previously-filed Teschner declaration is not persuasive because "it is not clear how the parameters of the invention as claimed are applied to this example [the comparative example in the declaration]." This statement is not understood by applicant, however.

Appendix B of the Teschner declaration indicates that the experiment followed the protocol of Example I of the '115 patent. At the end of Appendix B, it is explained that the caprylate precipitation and diafiltration removal process of the '115 patent resulted in not only the removal of citrate, but 80% of the protein as well -- meaning that the '115 patent provides a very inefficient approach. See Teschner declaration at paragraph 7 and Appendix B at paragraphs 5 and 6.

More specifically, the '115 patent prescribes a caprylate precipitation approach, as explained at column 5, lines 49-54, and this precipitation does not result in the reduction of citrate. Please compare the citrate values for "IV-I-supernatant" and "centr. supernatant" in paragraph 8 of Appendix B," which are respectively 8.05 mmol/l and 8.93 mmol/l of citrate. It is only the later diafiltration that removes citrate. In contrast, applicant's use of a caprylate and the like in an exchange context under non-precipitating conditions allows for the efficient displacement of citrate by caprylate and the like, which results in greater protein yield while providing a medicament that is low in citrate. A low citrate medicament will not unduly extract undesired metals from glass containers.

Applicant therefore submits that the process and resulting product of the '115 patent are very different from the claimed invention, and therefore this patent

cannot anticipate the instant claims. Applicant therefore respectfully requests withdrawal of the rejection.

Turning to the next rejection, the '997 patent discloses the use of dealkalized soft glass containers having low metal content, which would minimize the leaking of metals into a medicament. However, the '997 patent is absolutely silent on the issue of citrate and the problems it can cause in metal-containing hard glass, which is a problem addressed by the present invention. See paragraph 9 of the Teschner declaration. Thus, the '997 patent does not teach how to exchange citrate in order to prevent it from extracting undesired metals from hard glass containers. The '997 patent bears not even a slight resemblance to the claimed invention, and thus this patent cannot anticipate the claims.

Given the above distinctions, applicant submits that the '115 and '997 patents do not meet the limitations of the claims, and thus do not enable the practice of the claimed invention. Accordingly, the '115 and '997 patents do not place the claimed invention in the possession of the public, and therefore the rejections should be withdrawn.

The claimed invention is not suggested by the prior art

On pages 5-6 of the office action, the examiner rejected claims 14-18, 20-29, 31, 33 and 34 as obvious over the '115 patent or the '997 patent and U.S. Patent No. 5,118,794. Also, the examiner rejected claims 14-18, 20-31, 33 and 34 as obvous over U.S. Patent No. 5,229,498 in view of the '997 patent. Applicant

respectfully traverses these rejections. The examiner did not expand on her use of the '498 and '794 patents. The deficiencies of the '115 and '997 patents are explained in detail above, and will be repeated here in only summary fashion.

Turning to the first obviousness rejection, the examiner combines the '794 patent with the '115 and '997 patents. The '794 patent discloses the use of heat treatment to inactivate viruses in albumin solutions. The '794 patent also discloses the use of stabilizers and surfactants to preserve albumin in solution. However, the '794 patent makes no mention of citrate, exchange of citrate or minimizing the leakage of undesired metals from glass containers to medicaments contained therein. Accordingly, the '794 patent does not rectify the deficiencies of the '115 patent (use of caprylate as a precipitator rather than a citrate exchanger) and '997 patent (reliance on low metal soft glass rather than exchange of citrate). Accordingly, applicant submits that the first rejection does not satisfy the requirements of a *prima facie* case, and therefore the rejection should be withdrawn.

Turning to the second rejection, the '498 patent concerns the exchange of multivalent metal cations (i.e., aluminum) with monovalent metal cations (i.e., sodium or potassium). Applicant's invention, however, exchanges citrate and optionally citrate-bound metals for mono- and/or dicarboxylates, and/or their acids, as recited in the claims. Thus, the '498 patent describes a completely different methodology than the claimed invention, and therefore the combination of the '498 patent with the '997 patent does not provide all the elements recited in the claims.

Accordingly, the combination of the '498 and '997 patents cannot rendered the claimed subject matter obvious. Applicant therefore requests withdrawal of the rejection.

The invention achieves superior and surprising results

The claimed invention surprisingly allows for the minimization of citrate and the avoidance of undesired metal contamination, all while being readily adaptable to be integrated into established production facilities. See specification at pages 5-6. Such an approach could not be presaged by the prior art.

The superior and surprising results obtained with the present invention further establish patentability, and the examiner has not demonstrated anything to the contrary. *See U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); MPEP § 716.02 (August 2001). As explained by the Federal Circuit:

> [W]hen an applicant demonstrates *substantially* improved results ... and *states* that the results were *unexpected*, this should suffice to establish unexpected results *in the absence of* evidence to the contrary.

In re Soni, 34 USPQ2d 1684, 1688 (Fed. Cir. 1995) (emphasis in original).

Applicant thus submits that the surprising results achieved by the invention provide further support for patentability.

Request

Applicants submit that the claims are in condition for allowance, and respectfully request favorable consideration to that effect. The examiner is invited to contact the undersigned at (202) 912-2000 should there be any questions.

Respectfully submitted,

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MARKED UP COPY OF AMENDED CLAIMS

14. (Twice amended) A method of preparing a plasma-protein-containing medicament **using as a starting material one** selected from the group consisting of citrated plasma and a citrate-containing plasma fraction, wherein (I) said medicament is substantially free from undesired metals selected from the group consisting of aluminum, cadmium, zinc, lead and iron, and (II) said medicament does not take up any **undesired** metals when stored in metal-containing containers, ~~wherein said method comprises~~

exchanging citrate and optionally citrate-bound metals in a plasma-protein-containing solution for one selected from the group consisting of a water-soluble monocarboxylate, a water-soluble dicarboxylate, a monocarboxylic acid and a dicarboxylic acid, wherein the exchanging occurs under non-precipitating conditions,

recovering at least one plasma protein, and

finishing said medicament.

15. (Twice amended) **The [A]** method as set forth in claim 14, wherein said at least one plasma protein recovered is selected from the group consisting of the factors of coagulation, **[and] factors of** fibrinolysis, immunoglobulins, glycoproteins and albumin.

16. (Three Times Amended) **[A]** **The** method as set forth in claim 14, wherein **[said exchanging of said citrate and optionally of said citrate-bound metals is performed using a salt of said monocarboxylate, dicarboxylate, monocarboxylic or dicarboxylic acid and said]** monocarboxylate, dicarboxylate, monocarboxylic **acid**or dicarboxylic acid has 2 to 20 carbon atoms.

17. (Twice amended) **[A]** **The** method as set forth in claim 14, wherein said exchanging of said citrate and optionally of said citrate-bound metals is performed using at least one substance selected from the group consisting of a caprylate and a tartrate.

18. (Twice amended) **[A]** **The** method as set forth in claim 14, wherein said exchanging of said citrate and optionally of said citrate-bound metals is performed using a monocarboxylic or dicarboxylic acid having 2 to 4 carbon atoms.

20. (Twice amended) **[A]** **The** method as set forth in claim 14, wherein said exchanging of said citrate and optionally of said citrate-bound metals **is** performed during one of a diafiltration, ultrafiltration, gel permeation chromatography and a chromatographic separation method.

21. (Twice amended) **[A]** **The** method as set forth in claim 14, further comprising subjecting said plasma-protein-containing solution to at least one of a

purification and a concentration procedure before said exchanging of said citrate and optionally of said citrate-bound metals.

22. (Twice amended) **[A] The** method as set forth in claim 14, further comprising subjecting said plasma-protein-containing solution to a treatment for virus inactivation.

23. (Twice amended) **[A] The** method as set forth in claim 22, wherein said treatment for virus inactivation is performed before said exchanging of said citrate and optionally of said citrate-bound metals.

24. (Twice amended) **[A] The** method as set forth in claim 22, wherein said treatment for virus inactivation is performed after said exchanging of said citrate and optionally of said citrate-bound metals.

25. (Twice amended) **[A] The** method as set forth in claim 22, wherein said treatment for virus inactivation is performed before and after said exchanging of said citrate and optionally of said citrate-bound metals.

26. (Amended) **[A] The** method as set forth in claim 22, wherein said treatment for virus-inactivation is a heat-treatment.

27. (Twice amended) **[A] The** method as set forth in claim 22, wherein said treatment for virus inactivation is performed immediately after said recovering of at least one plasma protein in the presence of the monocarboxylate or dicarboxylate.

28. (Twice amended) **[A] The** method as set forth in claim 14, wherein the finishing of said medicament is performed using only citrate-free components.

29. (Twice amended) **[A] The** method as set forth in claim 14, wherein said exchanging of said citrate and optionally of said citrate-bound metals is performed in the presence of sodium chloride.

30. (Amended) **[A] The** method as set forth in claim 29, wherein said sodium chloride is an at least 4% by weight sodium chloride solution.

31. (Twice amended) A plasma-protein-containing medicament **using as a starting material one** selected from the group consisting of citrate plasma and a citrate-containing plasma fraction, wherein the medicament is (I) substantially free from undesired metals selected from the group consisting of aluminum, cadmium, zinc, lead and iron, and (II) said medicament does not take up any **undesired** metals when stored in metal-containing containers, wherein the medicament is **[obtainable] obtained** by

exchanging citrate and optionally citrate-bound metals in a plasma-protein-containing solution for one selected from the group consisting of a water-soluble monocarboxylate, a water-soluble dicarboxylate, a **water-soluble** monocarboxylic acid and a **water-soluble** dicarboxylic acid, wherein the exchanging occurs under non-precipitating conditions,

recovering at least one plasma protein, and

finishing said medicament, wherein

said medicament has a content of undesired metals of less than 100 µg/1.

33. (Amended) **[A] The** plasma-protein-containing medicament as set forth in claim 31, wherein said content of undesired metals is less that 10 µg/l.

34. (Twice amended) **[A] The** plasma-protein-containing medicament as set forth in claim 31, wherein said content of undesired metals is less than 200 ng/1.